

Evidence for an unfolded border-collision bifurcation in paced cardiac tissue

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Abstract

We investigate, both experimentally and theoretically, the bifurcation to alternans in heart tissue. Previously, this phenomenon has been modeled either as a smooth or as border-collision period-doubling bifurcation. Using a new experimental technique, we find a hybrid behavior: very close to the bifurcation point the dynamics are smooth-like, whereas further away they are border-collision-like. This behavior is captured by a new type of model, called an unfolded border-collision bifurcation.

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Many nonlinear systems display a bifurcation, where the system's response changes qualitatively as an adjustable parameter - the bifurcation parameter - is varied [1]. Bifurcation theory provides useful tools to understand the behavior of the system in the vicinity of the bifurcation. The most widely investigated nonlinear systems are those described by smooth differential equations or maps. As a result, there exists a vast literature on the classes of bifurcations occurring in these systems. On the other hand, bifurcations occurring in piecewise smooth systems, such as border-collision bifurcations, are still under investigation and are known to display much richer behaviors [2]. Border-collision bifurcations are believed to occur in a variety of systems, such as mechanical and electrical devices that involve sudden switching of a component, and in economic systems where decisions are made when a variable crosses a threshold.

The primary purpose of this Letter is to describe experimental observations and a resulting new model of the bifurcation to alternans (defined below) in paced bullfrog cardiac muscle. We find that the bifurcation mediating this transition displays both smooth and piecewise-smooth characteristics. Specifically, by investigating the system's sensitivity to perturbations, we find smooth-like behavior near the bifurcation point while, further away, the behavior is border-collision like. This apparently contradictory behavior is placed in the context of a new type of model, which we call an unfolded border-collision bifurcation. The bifurcation to alternans is a crucial problem to study because there is evidence that it can initiate ventricular fibrillation [3, 4, 5], which often underlies sudden cardiac death, one of the leading causes of death in the United States [6]. Therefore, determining the type of bifurcation is a crucial step in reaching the ultimate goal of suppressing cardiac alternans [7].

Before describing our findings, we review briefly the behavior of paced cardiac muscle. An applied electrical stimulus induces an action potential, which is the characteristic time course of the transmembrane voltage. In experiments, the dynamical state of the tissue is often described by measuring the action potential duration (APD). The pacing interval, known as the basic cycle length (B), serves as the bifurcation parameter. Under various conditions of periodic electrical pacing, M stimuli can elicit N responses (M:N behavior) for different values of B, where the transition from one response pattern to another under changes in B is mediated by a bifurcation. For slow pacing, 1:1 behavior is usually observed, where each action potential is identical. As B shortens, a period-doubling bifurcation sometimes occurs

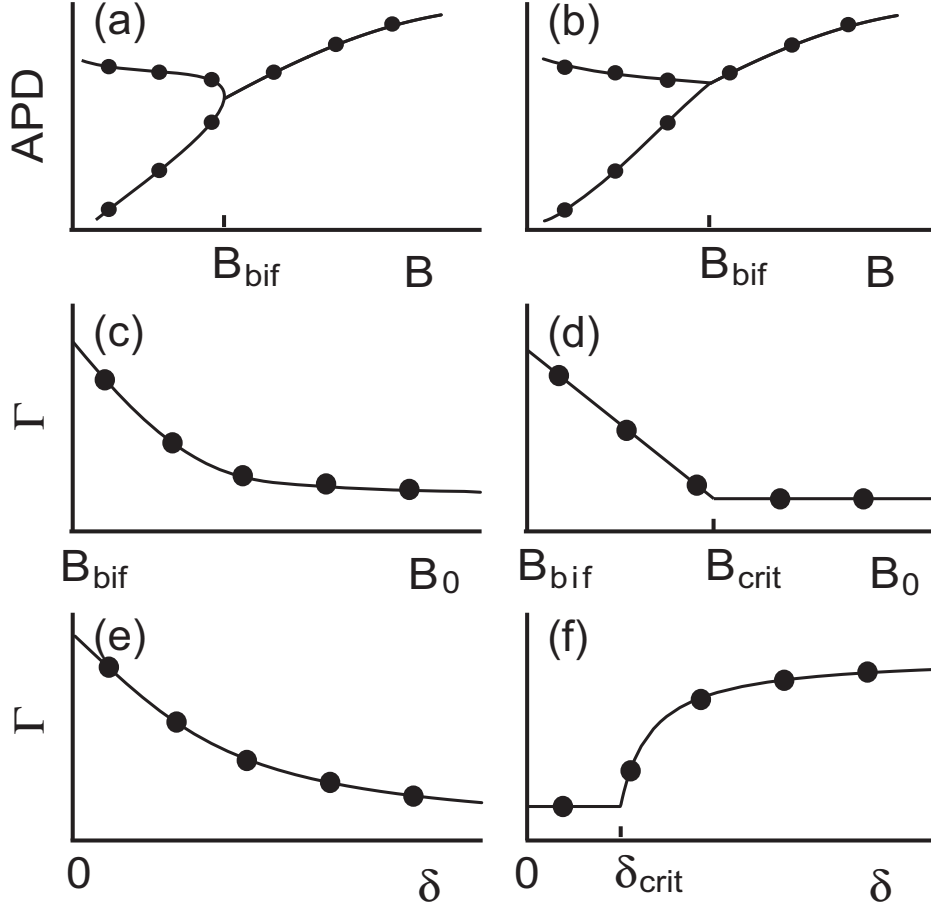


FIG. 1: Schematic bifurcation diagrams with discrete sampling. The sampled points (solid dots) are identical for the (a) smooth and (b) border-collision bifurcation. (c-f) Alternate pacing: the trend in Γ vs. B is illustrated for a (c) smooth and (d) border-collision bifurcation and the trend in Γ vs. δ is illustrated for a (e) smooth and (f) border-collision bifurcation.

[8], giving rise to a long-short periodic pattern in APD known as a 2:2 rhythm or alternans [9].

Beginning with the pioneering work of Nolasco and Dahlen [10], it is generally believed that the transition to alternans is due to a smooth supercritical period-doubling bifurcation. More recently, Sun *et al.* [11] introduced a model for atrioventricular nodal conduction in which it has been shown [7, 12] that the transition to alternans arises from a border-collision bifurcation. The bifurcation diagrams, where the steady-state values of APD are plotted as a function of B , are different for these two cases. For a smooth period-doubling bifurcation, the bifurcated curves become tangent at the bifurcation point, as shown in Fig.

1(a), whereas they are generally not tangent for a border-collision bifurcation, as shown in Fig. 1(b). Unfortunately, it is exceedingly difficult to measure the bifurcation diagram with sufficient resolution to distinguish between these behaviors experimentally because only a finite number of pacing intervals can be tested before tissue damage occurs. For example, Figs. 1(a) and (b) show that the same set of data (solid dots) is consistent with both types of models.

We apply a new technique involving alternate pacing [13] to investigate the bifurcation type in cardiac tissue. This method is a modification of a technique introduced by Heldstab *et al.* [14] for general dynamical systems. Specifically, this method relies on periodic perturbations to the bifurcation parameter to investigate the dynamics of the system in the 1:1 region. More recently, Karma and Shiferaw [15] suggest that Heldstab's method [14] can be exploited in a clinical setting to study the likelihood of an unfavorable cardiac event.

Our alternate pacing protocol is implemented in the following way. In the 1:1 regime, we perturb the nominal pacing interval B_0 by a small value δ so that, for the n^{th} stimulus,

$$B_n = B_0 + (-1)^n \delta. \quad (1)$$

As a result, APD alternates in a long-short pattern with the corresponding steady-state values denoted by APD_{long} and APD_{short} . To measure the system's sensitivity to perturbations, we define a gain as

$$\Gamma = \frac{APD_{\text{long}} - APD_{\text{short}}}{2\delta}. \quad (2)$$

In previous papers [13, 16], we have shown that, for the two types of bifurcations, Γ depends on the bifurcation parameter B_0 and perturbation amplitude δ in qualitatively different ways. Specifically, we computed Γ under variations of both B_0 and δ . For a smooth bifurcation, Γ decreases monotonically as B_0 increases compared to B_{bif} [see Fig. 1(c)]. This is because the bifurcation parameter's sensitivity to perturbations decreases further away from the bifurcation point. Likewise, Γ decreases monotonically as δ increases [see Fig. 1(e)]. Specifically, Γ is proportional to $\delta^{-2/3}$ for a range of δ , and it saturates for sufficiently small δ [16]. On the other hand, for a border-collision bifurcation, Γ is a piecewise smooth function of B_0 and δ . Overall, when the alternating response crosses the border (which occurs at B_{crit} and δ_{crit}), Γ exhibits a decreasing trend as B_0 increases [see Fig. 1(d)] but an increasing trend as δ increases [see Fig. 1(f)] [17]. Although Figs. 1(c) and (d) are slightly different, it is difficult to distinguish their differences with discretely-

sampled data. However, because of significant dissimilarity between Figs. 1(e) and (f), the distinction between the two bifurcation types is evident even with just a few data points and in the presence of experimental noise.

We apply the alternate pacing protocol in 6 adult bullfrogs. In these experiments, the heart is excised from an adult bullfrog (*Rana catesbeiana*) of either sex. After the pacemaker cells are cut away, the top half of the ventricle is removed and placed in a chamber that is superfused with a recirculated physiological solution [8]. A bipolar extracellular electrode applies 2-ms-long rectangular current pulses to the epicardial surface of the tissue [18]. The current, whose typical amplitude is twice the value needed to elicit a response for slow pacing, activates a propagating excitation wave. Transmembrane voltage is measured with a glass microelectrode filled with KCl conducting fluid. Before collecting any data, the tissue is paced at $B_0 = 1,000$ ms for about 30 minutes. We collect data at a sampling rate of 4 kHz. The data is then processed in custom-written Matlab code.

We implement the alternate pacing protocol experimentally by repeatedly carrying out the following steps: 1) We pace at B_0 for two minutes, during which we record the transient behavior of the APDs as they reach a steady-state of either a 1:1 or 2:2 rhythm; 2) We perturb B_0 for 20 seconds at one value of δ and record the subsequent APDs; 3) We repeat step 2 three more times, each time with a new δ value (for 11 of the 12 trials, the values of δ sweep from high to low, to include 20 ms, 15 ms, 10 ms and 5 ms; in one trial, we use the reverse.); and 4) The perturbations are turned off and pacing at B_0 is resumed for 20 seconds to check that the steady-state value of the system did not drift. The preceding steps are repeated for decreasing values of B_0 until persistent alternans over several B_0 s ensue, or the cell fails to respond to every applied stimuli. Twelve of our trials exhibited a transition to alternans. Typically, B_0 is decreased in steps of 25 ms, which means that the last B_0 with a 1:1 response is within 25 ms of B_{bif} .

To analyze the results, we determine Γ vs. δ at each B_0 . In 4 trials from three frogs, we find that Γ shows a *decreasing* trend as δ increases, where a typical example is shown in Fig. 2(a), which agrees with a smooth bifurcation [recall Fig. 1(e)]. However, 4 other trials from two frogs demonstrate an *increasing* trend in Γ as δ increases, where a typical example is shown in Fig. 2(b), which agrees with a border-collision bifurcation [recall Fig. 1(f)]. In three other trials from three frogs there is no significant variations in Γ for different δ 's and therefore cannot be classified into either category. The remaining trial is discussed in

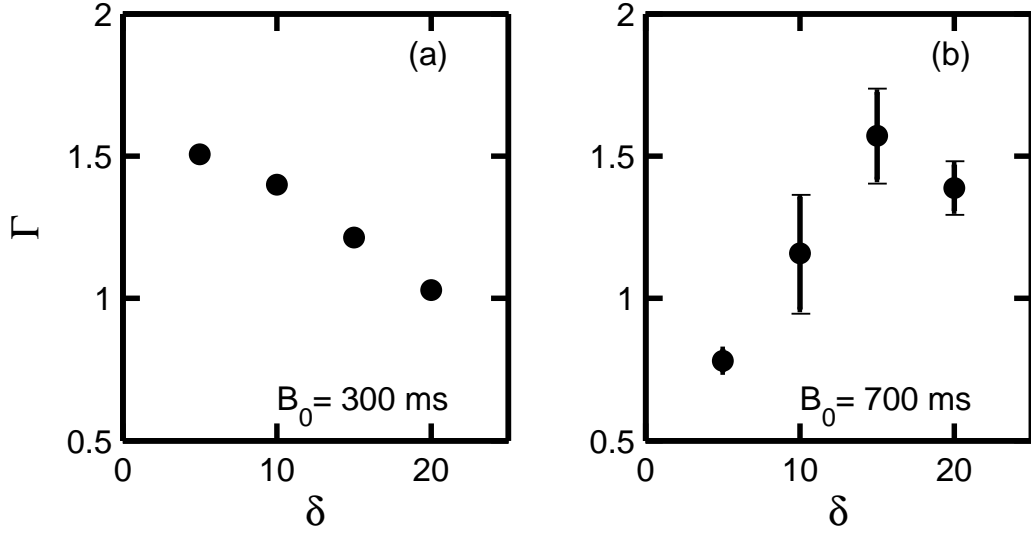


FIG. 2: Typical experimental results displaying two different trends in Γ vs. δ as revealed by alternate pacing for two different frogs. The trend is consistent with (a) a smooth period-doubling bifurcation and (b) a border-collision bifurcation.

detail below. For all experimental data in this paper, the error bars represent the statistical and systematic error in the measurement of APD. In the cases where the error bars are not evident, the error is smaller than the symbol size.

Surprisingly, in the remaining experimental trial, we see a smooth behavior when $B_0 - B_{\text{bif}} \approx 25 \text{ ms}$, but a border collision behavior when $B_0 - B_{\text{bif}} \approx 50 \text{ ms}$, as shown in Figs. 3(b) and (c), respectively. These results are unanticipated because we expected to find evidence supporting either one or the other of the two theorized bifurcation types. Figure 3(a) shows Γ vs. B_0 for different values of δ , where it is seen that these curves cross one another. This crossing is not indicative of either a smooth or border-collision period-doubling bifurcation, and is one of our primary experimental results.

We find that these seemingly contradictory observations can be explained by a mathematical model that unfolds a border-collision bifurcation. Consider iterations of the skewed tent map (in one dimension)

$$x_{n+1} = \mu - \alpha x_n - \beta |x_n|, \quad (3)$$

which is singular at the border $x = 0$ in state space. This map exhibits a border-collision period-doubling bifurcation under the condition: $-1 < \alpha + \beta < 1 < \alpha - \beta$ and $-1 < \alpha^2 - \beta^2 < 1$.

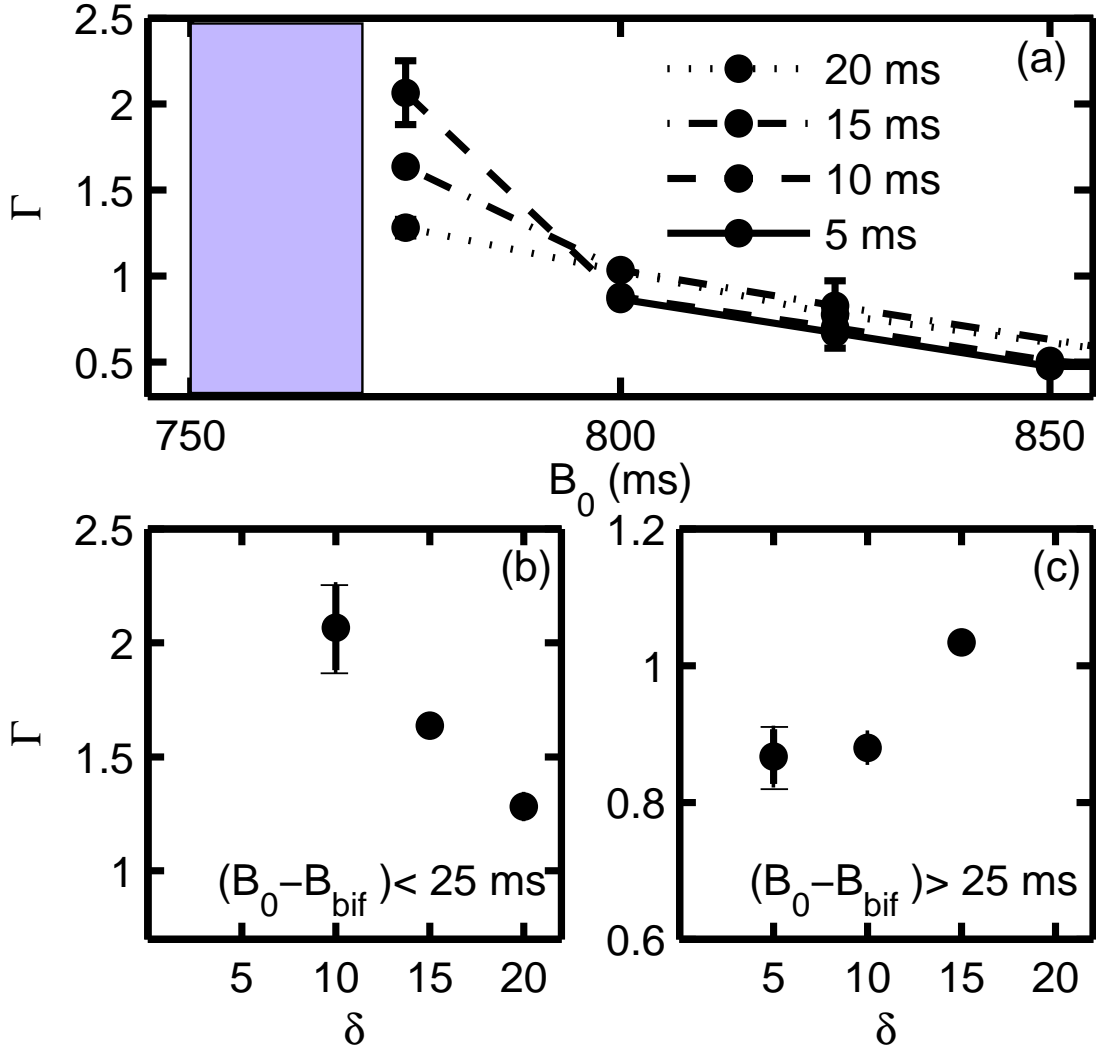


FIG. 3: Experimental evidence for both a smooth and border-collision bifurcation in a single trial. (a) The trend in Γ vs. B_0 for four different values of δ (legend). Note that the curves cross, indicating the transition from border-collision to smooth dynamics. The bifurcation occurs somewhere in the gray area, whose precise location cannot be determined because of our finite sampling. The same data is replotted in (b) and (c). The behavior in (b), where $(B_0 - B_{bif}) < 25$ ms, is consistent with a smooth bifurcation and in (c), where $25 \text{ ms} < (B_0 - B_{bif}) < 50$ ms, is consistent with a border-collision bifurcation.

1. Replacing $|x|$ by $\sqrt{x^2 + \varepsilon^2}$, where ε is a small parameter, results in an unfolding of the piecewise-smooth map (3)

$$[floatfix]x_{n+1} = \mu - \alpha x_n - \beta \sqrt{x_n^2 + \varepsilon^2}. \quad (4)$$

This new map can be viewed as an approximation of the skewed tent map (3). In the limit $\varepsilon \rightarrow 0$, map (4) reduces to map (3). Map (3) exhibits a border-collision period-doubling bifurcation while, for $\varepsilon \neq 0$, the unfolded map (4) exhibits a smooth period-doubling bifurcation. However, the dynamics of map (3) and map (4) exhibit no significant differences except when μ is less than or on the order of ε .

We investigate map (4) with $\alpha = 2.5$, $\beta = -2.3$, and $\varepsilon = 0.01$. The dynamical variable is x (similar to APD) and the bifurcation parameter is μ (similar to B_0). With this nonzero ε , the bifurcation of map (4) occurs earlier than for map (3), specifically at $\mu_{\text{bif}} = -0.0091$ rather than for $\mu_{\text{bif}} = 0$ for map (3). We apply the alternate pacing protocol to map (4) by perturbing μ with $(-1)^n \delta$. Figure 4(a) shows Γ vs. μ for different values of δ . These curves cross one another [19]. Although the bifurcation is smooth at sufficiently small scales, it shows behavior qualitatively similar to a border-collision bifurcation when $\mu > 0$, in good agreement with our experimental findings [see Fig. 3(a)]. In Figs. 4(b) and (c), Γ vs. δ is plotted for $\mu = -0.00773$ and $\mu = 0.01$, respectively. For negative values of μ , Γ decreases as δ increases, a trend consistent with a smooth bifurcation [see Fig. 4(b)]. On the other hand, for positive values of μ , Γ increases as δ increases, a trend consistent with a border-collision bifurcation [see Fig. 4(c)]. We note that the region over which the dynamics are smooth-like [$\mu < 0$ in Fig. 4(a)] can be very small and on the order of ε in width. Therefore, a smooth bifurcation may be masked by a border-collision bifurcation, depending on the proximity to the bifurcation point.

Our results call to question the suggested clinical use of alternate pacing [15]. In a typical smooth bifurcation, one expects large Γ s far above the bifurcation point. Hence, the propensity for alternans could be revealed using alternate pacing for values of B_0 far from the bifurcation. It was suggested [15] that such a procedure might be useful in the clinic because it would use pacing rates that are slow enough to avoid a potentially life-threatening situation. However, we find that Γ remains small until the pacing rates are decreased to a neighborhood of the bifurcation. Consequently, our research suggests that one would not be able to probe instabilities clinically through the use of alternate pacing.

Our experimental results reveal that the bifurcation, although smooth on a fine scale, may exhibit behavior similar to a border-collision bifurcation on a coarse scale. This phenomenon is described by a new model called an unfolded border-collision bifurcation. We speculate that the origin of this behavior is due to rapid changes in cellular behavior during the course of the action potential [20], such as those in the current-voltage or the current-concentration relation [21].

Acknowledgments

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- [18] All procedures are approved by the Duke University Institutional Animal Care and Use Committee (DIACUC).
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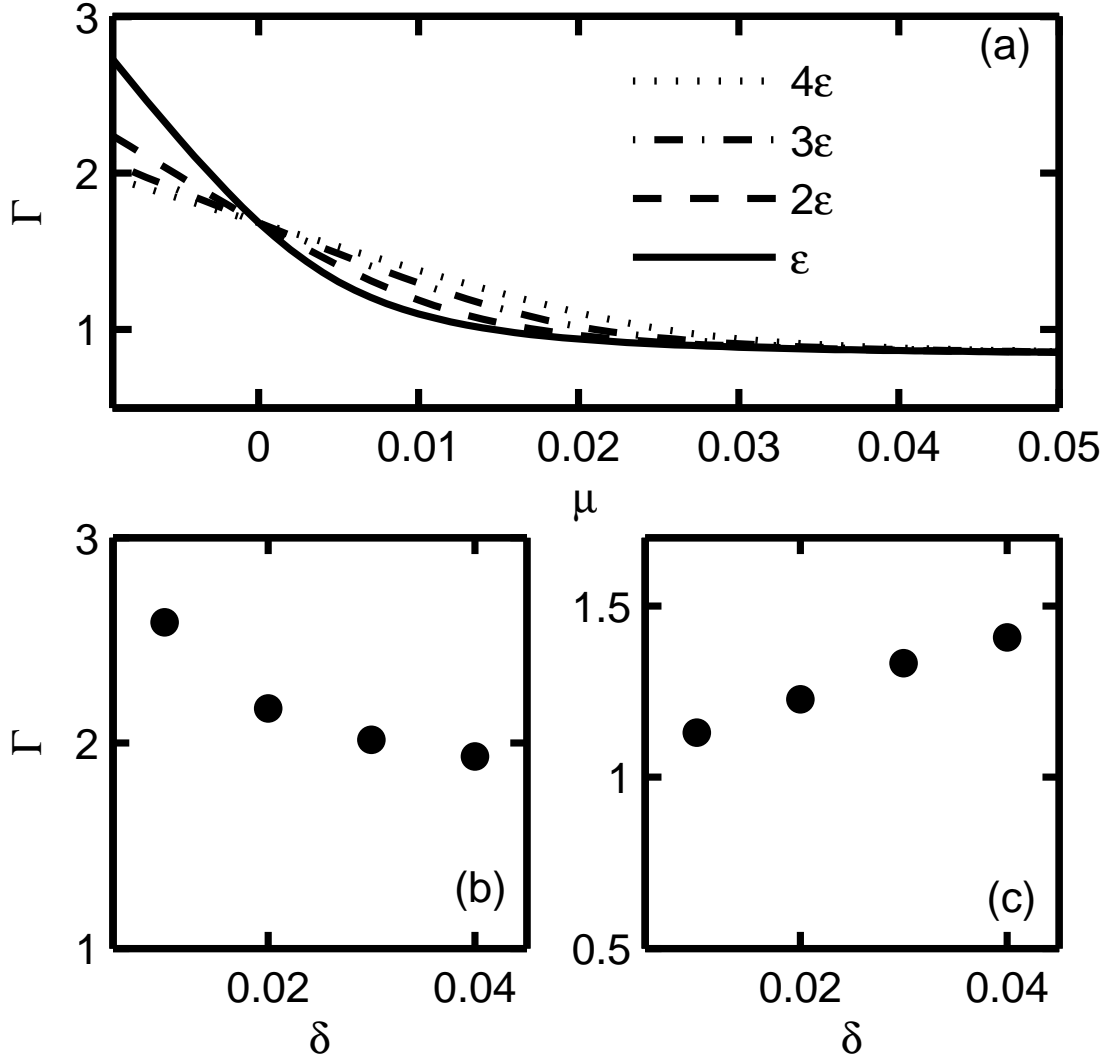


FIG. 4: Theoretically predicted behavior of the unfolded border-collision bifurcation [map (4)]. (a) Γ as a function of the bifurcation parameter μ for various values of the perturbation size δ (legend, $\epsilon = 0.01$). The same data is replotted in (b) and (c). Γ vs. δ for (b) $\mu = -0.0073$, a distance of 0.0018 from the bifurcation point and (c) $\mu = 0.01$, a distance of 0.0191 from the bifurcation point. The trend in Γ vs. δ is consistent with a smooth bifurcation in case (b) and a border-collision bifurcation in case (c).